REMARKS

The final Office Action dated April 2, 2004, has been carefully considered. Claims 1-22 are pending in the present application. Claims 23-29 have been canceled without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in a continuation or divisional application. Claims 1 and 12 have been amended to clarify the claim language. In particular, claims 1 and 12 have been amended herein to recite "a prefabricated tubular metal sidewall structure having open ends and openings in the sidewall structure". This amendment is fully supported by the originally filed specification and does not introduce new matter. It is believed that the claim amendments would not raise new issues that would require further consideration and/or search.

Applicants thank Examiner Landrem and Examiner Willse for the courtesy of the personal interview of August 24, 2004, granted to Linda Azrin (Reg. No. 44,516), Catharina Chin Eng (Reg. No. 42,412), and Scott Bluni (Reg. No. 40,916), during which the final Office Action and pending claims were discussed. The substance of the interview is incorporated into this Amendment.

Entry of the claim amendments and reconsideration and allowance of the present application in view of the following remarks are respectfully requested.

I. CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

A. Claims 1, 3, 8, 10-12, 14, 19, 21, And 22 Are Patentable Over U.S. Patent 5,545,208 To Wolff *et al.* ("Wolff") In View Of U.S. Patent No. 6,558,733 B1 To Hossainy *et al.* ("Hossainy)

Claims 1, 3, 8, 10-12, 14, 19, 21, and 22 have been rejected under 35 U.S.C. § 103(a) as allegedly being anticipated by Wolff in view of Hossainy. This rejection is respectfully traversed.

The inventions of independent claims 1 and 12 are directed to an expandable stent for implantation in a patient comprising a prefabricated tubular metal sidewall structure having open ends and openings in the sidewall structure. A coating is disposed on a surface of the prefabricated sidewall structure, wherein the coating comprises a hydrophobic biostable elastomeric material and a biologically active material. Claim 1 also recites that the coating continuously conforms to the structure in a manner that preserves the openings. Claim 12 also recites that the openings are substantially free of webbing. Claims 3, 8, 10, and 11 depend from claim 1, and thus also include all the recitations of claim 1. Claims 14, 19, 21,

and 22 depend from claim 12, and thus also include all the recitations of claim 12. As explained in the present application, the tubular body "is formed of an open braid of fine single or polyfilament metal wire." (Specification, page 3, lines 32-33). In addition, "[t]he coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved, in the coated device." (Specification, page 4, lines 18-21).

As discussed in the Response filed on November 26, 2003, and during the August 24, 2004 interview, and as acknowledged by the Examiner in the present Office Action, Wolff does not disclose or suggest a prefabricated tubular metal sidewall structure. Accordingly, Wolff also does not disclose or suggest a coating comprising a hydrophobic biostable elastomeric material and a biologically active material that is disposed on the surface of the prefabricated tubular metal sidewall structure.

In contrast, Wolff discloses a stent that includes drug eluting filaments that are braided together to form a stent. (Col. 7, lines 7-23). The "filaments could be impregnated with a drug and biodegradably elute." (Col. 7, lines 20-21). A single filament could be braided into the stent or varying numbers of strands that are drug-eluting could be braided into a filament that forms the stent. (Col. 7, lines 7-23). Thus, in Wolff the filaments include a drug or are coated with a drug before the filaments are woven together. Wolff discloses that "[i]n all cases, the prostheses of [Wolff's] invention require the presence of an elutable drug compounded to the prosthesis itself." (Col. 2, lines 12-14. (Emphasis added)). Thus, the drug coating is not applied to a prefabricated stent, but incorporated into the filaments themselves before the filaments are formed into a stent.

Wolff discloses that "[w]ith conventional metal stents, the invention requires a drug-carrying coating overlying at least a portion of the metal." (Col. 2, line 14-16). However, as explained above, Wolff does not disclose or suggest that the coating is disposed on a prefabricated tubular metal sidewall structure of a stent. Instead, Wolff discloses a coating on individual filaments that are then woven together. Wolff discloses that the "exterior surface of the metal filaments 22 would include a coating 14 with a drug-eluting polymer." (Col. 6, lines 60-61). Wolff also states that Fig. 13 shows a filament that is formed with a metal core 16 and a coating 14. (Col. 7, lines 33-34). But Wolff does not disclose or suggest that the filaments are formed into a sidewall structure and then coated with a biologically active material and a polymer. In fact, Wolff teaches away from a coating on a prefabricated

sidewall structure by disclosing individual filaments that are coated and then braided or woven or bonded together. (Col. 7, lines 7-36.)

Also, in referring to Figure 3B, Wolff expressly states that Figure 3B shows that "the *filament* 12 may be made from one or several layers of polymer." (Col. 9, lines 23-25). (Emphasis added). Wolff does not even use the term "coating" in discussing Figure 3B. Hence, this figure does not show a coating for the prosthesis but a filament or wire-like portion which forms a part of the prosthesis, *i.e.*, a substrate upon which a coating can be placed. Accordingly, items 14 and 15 shown in Figure 3B are *not* layers of a coating disposed on a prefabricated sidewall of a stent but are instead layers of the filament used to form a prosthesis. Hence, instead of comprising a coating on a prefabricated sidewall of a stent, items 14 and 15 in Figure 3B describe a filament used to form the prosthesis. In contrast, Applicants' invention is directed to a stent having a prefabricated sidewall structure that is covered by a coating of a hydrophobic biostable elastomeric material and a biologically active material.

As discussed during the Interview, Wolff's device is structurally different than the stent of the present invention which comprises a prefabricated tubular metal sidewall structure and a coating disposed on a surface of the prefabricated sidewall structure.[1] As demonstrated during the Interview, because Wolff's device is formed by coating individual filaments and then weaving the filaments together, unlike the stent of the present invention, Wolff's device will have a double layer of coating between the overlapping filaments. This double layer of coating between the filaments will result in double dosing of the drug to a patient at certain parts of the stent. Thus, in contrast to the present invention, Wolff's device will not have a uniform coating as in the presently claimed invention. *See, e.g.*, Present Specification, page 10, lines 9-11 (". . . coat a metallic braided stent . . .in a manner which applies a thin, uniform coating . . . of the heparin/polymer mixture on the surfaces of the stent."); and page 11, lines 6-8 ("Fig. 4A depicts a stent which has been spray coated . . . to provide a thin, uniform coating on all surfaces of the stent."); and Fig. 4A. In addition, the

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[1] Applicants respectfully submit that "prefabricated tubular metal sidewall structure" is not a process limitation, and even if it were, such limitation imparts the presently claimed device with distinctive structural characteristics. As stated in the MPEP, "[t]he structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where . . . the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product." MPEP § 2113 *citing In re Garnero*, 412 F.2d 276, 279.

drug coating on each of the overlapping filaments can rub against each other once the stent is assembled and thereby affect the integrity of the coating and the device itself.

Furthermore, Wolff's device would be more difficult to manufacture. For example, once the filaments are coated it would be difficult to handle the drug-coated filaments and form a stent with minimal loss of coating material and risk of exposure. In addition, due to the rubbing of the coating between overlapping filaments, there is a greater risk of non-uniform drug delivery to the patient. Moreover, it is noted that Wolff's device (which is formed by coating filaments and then weaving the coated filaments together to form a stent) has not been commercialized, while the present invention has been widely commercialized.

Hossainy does not remedy the deficiencies of Wolff. Hossainy does not disclose or suggest "a coating disposed on a surface of said prefabricated sidewall structure" having openings therein, wherein the coating "continuously conforms to said structure in a manner that preserves said openings" as recited in claim 1, or wherein the "openings are substantially free of webbing" as recited in claim 12.

In contrast, Hossainy discloses a prosthesis, such as a stent, having a body structure that has "one or more micropatterned microdepots formed therein." (Col. 2, lines 35-42). Figs. 4a and 4b of Hossainy show such depots 30 on a stent 10. Hossainy states that the "depots have an open end, a closed end, and a diameter and a depth that is less than the thickness of the body structure of the prosthesis." (Col. 2, lines 42-44). Hossainy discloses that "various drugs or therapeutic substances may be loaded into the depots." (Col. 7, lines 54-55) (emphasis added). Hossainy further discloses that the "depots 30 are used to carry a variety of substances including . . . polymers impregnated with therapeutic substances." (Col. 4, lines 38-40) (emphasis added). Hossainy does not disclose or suggest that a therapeutic substance is contained anywhere other than in the depots that are formed in the stent.

Thus, Hossainy does not disclose or suggest that his therapeutic substance continuously conforms to the sidewall structure in a manner that preserves the openings therein as recited in claim 1 or that such substance is applied so that the openings in the sidewall structure are substantially free of webbing as recited in claim 12. Therefore, Hossainy does not disclose or suggest a coating comprising a hydrophobic biostable elastomeric material and a biologically active material on the surface of a prefabricated sidewall structure that has openings therein as presently claimed. In fact, by teaching that only the depots in the stent contain the therapeutic substance, Hossainy teaches away from a coating on the surface of a sidewall structure as presently claimed.

Moreover, there is no motivation to combine the teachings of Wolff and Hossainy to obtain the present invention where Wolff teaches away from a prefabricated sidewall structure having openings therein, and Hossainy teaches a prefabricated sidewall structure but teaches away from a coating on the surface of a prefabricated sidewall structure.

Accordingly, Wolff and Hossainy, either individually or in combination, do not disclose or suggest a coating that includes a hydrophobic biostable elastomeric material and a biologically active material that is disposed on a surface of a prefabricated tubular metal sidewall structure as required by the present claims.

Furthermore, the Examiner has stated that Hossainy "is used as a teaching to disclose that stents are prefabricated then coating applied" and to "teach coating a stent that is prefabricated." Office Action, page 5. Applicants respectfully submitted that Hossainy does not qualify as prior art as this claim language (recited in claims 1 and 12) finds support in prior application no. 08/663,490, filed June 13, 1996, and application no. 08/424,884, filed April 19, 1995, copies of which are attached hereto as Appendices A and B, respectively.[2] In particular, support in prior application no. 08/663,490 can be found at, for example, page 1, line 19; page 6, lines 6-7; page 7, lines 10-15; page 9, line 17; page 10, lines 25-28; page 22, lines 27-28; and page 24, lines12-14, which corresponds to page 1, lines 19-20; page 3, lines 30-31; page 4, lines 18-21; page 5, lines 19-20; page 6, lines 7-9; page 16, line 28; and page 17, lines 20-21 of the present application. Support in prior application no. 08/424,884, which is incorporated by reference into prior application no. 08/663,490 and the present application, can be found at, for example, page 5, lines 14-15; page 6, lines 2-6 and 9; page 7, lines 15-18; page 18, lines 4-5 and 20-22; page 20, lines 1-3; and Figs. 1A, 2A, 3 and 5A, which corresponds to page 3, lines 30-31; page 4, lines 18-21; page 5, lines 19-20; page 6, lines 7-9; page 16, line 28; page 17, lines 20-21; page 18, lines 5-6; and Figs. 1A, 2A, 3 and 5A of the present application.

Since Hossainy was filed on October 26, 2000, after the June 13, 1996 and April 19, 1995 filing dates of the parent application nos. 08/663,490 and 08/424,884, respectively, and

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[2] The present application is a Continuation-In-Part of copending application Serial No. 09/012,443, filed January 23, 1998, which is a Division of Serial No. 08/663,490, filed June 13, 1996, U.S. Patent No. 5,837,313, which is a Continuation-In-Part of Serial No. 08/526,273, filed September 11, 1995, abandoned, which is a Continuation-In-Part of Serial No. 08/424,884, filed April 19, 1995, abandoned. All portions of the prior applications not contained in the present application are deemed incorporated by reference. *See* First page. first paragraph of each application.

the present claim language allegedly disclosed by Hossainy finds support in those parent applications, Hossainy does not qualify as prior art.

Thus, it is believed that claims 1, 3, 8, 10-12, 14, 19, and 21-22 are patentable over Wolff and Hossainy. Reconsideration and withdrawal of this rejection, and allowance of claims 1, 3, 8, 10-12, 14, 19, and 21-22 are respectfully requested.

B. Claims 2, 4, 5, 13, And 15-16 Are Patentable Over Wolff In View Of Hossainy And Further In View of U.S. Patent No. 5,900,246 To Lambert ("Lambert")

Claims 2, 4, 5, 13, and 15-16 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wolff in view of Hossainy and further in view of Lambert. This rejection is respectfully traversed.

Claims 2, 4, and 5 depend from claim 1 which was shown above to be patentable over Wolff and Hossainy. Claims 13, 15, and 16 depend from claim 12 which was also shown above to be patentable over Wolff and Hossainy.

In addition, Wolff and Hossainy also do not disclose or suggest a thickness of a coating as recited in claims 2, 5, 13, and 16. With respect to claims 4 and 15, Wolff and Hossainy also do not even disclose or suggest a surface of a prefabricated sidewall structure comprising a coating. Thus, for these additional reasons, it is believed that claims 2, 4, 5, 13, and 15-16 are patentable over Wolff and Hossainy. Moreover, Hossainy does not qualify as prior art.

Lambert does not remedy the deficiencies of Wolff or Hossainy. Lambert discloses a stent coated with a polyurethane having a drug incorporated therein. Lambert does not teach an expandable stent or a stent having a sidewall structure having openings therein. Since Lambert does not disclose or suggest a sidewall structure having openings therein, Lambert fails to disclose or suggest a coated stent having a coating that continuously conforms to the structure in a manner that preserves the openings or a coated stent having openings substantially free of webbing as recited in the present claims. Moreover, there is no motivation to combine the teachings of Wolff and Lambert where Wolff teaches away from coating a prefabricated sidewall structure having openings therein, and Lambert does not even disclose or suggest a sidewall structure having openings therein and a coating that continuously conforms to the structure in a manner that preserves the openings or a coated stent having openings substantially free of webbing as recited in the present claims.

With respect to claims 4 and 15, the Examiner alleges that "Lambert further teaches that the composition of the polymer coating can have a 1:20 or 5% ratio of solvent to non-solvent to achieve the desired rate of evaporation (Column 4, lines 36-52) falling within the 4 to 6% range disclosed by the applicant." Office Action, page 3. However, claims 4 and 15 recite "about 4 to 6 w/v % dispersion of uncured hydrophobic biostable elastomeric material in a solvent. Lambert is referring to a ratio of a polymer solvent to a polymer non-solvent, not to a ratio of hydrophobic biostable elastomeric material (polymer) to a solvent. Thus, Lambert does not disclose or suggest "about 4 to 6 w/v % dispersion of uncured hydrophobic biostable elastomeric material in a solvent" as recited in claims 4 and 15.

For the above reasons, Wolff, Hossainy and Lambert, either individually or in combination, do not disclose or suggest a coating disposed on a prefabricated sidewall structure having openings therein as recited in the present claims. Moreover, there is no motivation to combine the teachings of Wolff, Hossainy, and Lambert to obtain the present invention where Wolff teaches away from coating a prefabricated sidewall structure having openings therein, Hossainy teaches away from a surface of a sidewall structure comprising a coating, and Lambert does not even disclose or suggest a prefabricated sidewall structure having openings therein. In addition, Hossainy does not qualify as prior art.

Accordingly, it is believed that claims 2, 4, 5, 13, and 15-16 are patentable over Wolff in view of Hossainy and further in view of Lambert. Reconsideration and withdrawal of this rejection, and allowance of claims 2, 4, 5, 13, and 15-16 are respectfully requested.

C. Claims 6, 7, 9, 17-18, And 20 Are Patentable Over Wolff In View Of Hossainy And Further In View Of U.S. Patent No. 5,464,650 to Berg *et al.* ("Berg")

Claims 6, 7, 9, 17-18, and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wolff in view of Hossainy and further in view of Berg. This rejection is respectfully traversed.

Claims 6, 7, and 9 depend from claim 1, and claims 17, 18, and 20 depend from claim 12. Claims 1 and 12 were shown above to be patentable over Wolff and Hossainy, and thus the dependent claims are also believed to be patentable over Wolff and Hossainy. As stated above, there is no motivation to combine the teachings of Wolff and Hossainy to obtain the present invention where Wolff teaches away from a prefabricated sidewall structure having openings therein, and Hossainy teaches away from a coating on the surface of a prefabricated sidewall structure. With respect to claims 6, 7, 17, and 18, Wolff does not disclose or suggest

a prefabricated sidewall structure comprising a coating, and Hossainy does not even disclose or suggest a coating as discussed above. In addition, Wolff does not disclose or suggest the metals recited in claims 9 and 20. Thus, it is believed that claims 6, 7, 9, 17, 18, and 20 are patentable over Wolff and Hossainy for these additional reasons. Moreover, Hossainy does not even qualify as prior art as discussed above.

Berg does not remedy the deficiencies of Wolff or Hossainy. Unlike the present invention, Berg does not describe or suggest a coated stent having openings therein, wherein the coating continuously conforms to the structure in a manner that preserves the openings or wherein the openings are substantially free of webbing as recited in the present claims. Berg is completely silent as to whether the openings in its stent contain a webbing of coating material. Furthermore, one of ordinary skill in the art would not be motivated to combine Berg with Wolff where Wolff teaches away from a prefabricated sidewall structure comprising a coating.

One of ordinary skill in the art would also not be motivated to combine the teachings of Wolff, Hossainy, and Berg, particularly where Wolff teaches away from a prefabricated sidewall structure comprising a coating and Hossainy teaches away from a coating on the surface of a sidewall structure. In addition, Hossainy does not qualify as prior art.

Accordingly, it is believed that claims 6, 7, 9, 17-18, and 20 are patentable over Wolff in view of Hossainy and further in view of Berg. Reconsideration and withdrawal of this rejection, and allowance of claims 6, 7, 9, 17-18, and 20 are respectfully requested.

D. Claims 23-29 Are Patentable Over Lambert In View of Hossainy

Claims 23-29 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lambert in view of Hossainy. Although Applicants disagree with this rejection, claims 23-29 have been cancelled without prejudice. The cancellation of claims 23-29 obviates this rejection.

II. CONCLUSION

As all rejections are believed to be overcome, all claims are believed to be in condition for allowance. Reconsideration and allowance of the present application are respectfully requested. An early notice to that effect would be appreciated. Should the Examiner not agree with Applicants' position, then a personal or telephonic interview is

respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

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Date: September 14, 2004

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Appendix A
U.S. Patent Application No. 08/663,490

DRUG RELEASE STENT COATING PROCESS

BACKGROUND OF THE INVENTION

I. Cross-Reference to Related Applications

The present application is a Continuation-In-Part of copending application Serial No. 08/526,273, filed September 11, 1995, and a Continuation-In-Part of copending application Serial No. 08/424,884, filed April 19, 1995, all portions of the parent applications not contained in this application being deemed incorporated by reference for any purpose. Cross-reference is also made to application Serial No. 08/_____, entitled "DRUG RELEASE STENT COATING AND PROCESS", filed of even date and of common inventorship and assignee, that is also a Continuation-In-Part of both above-referenced patent applications. Any portion of that application that is not contained herein is also deemed to be incorporated by reference for any purpose.

II. Field of the Invention

The present invention relates generally to therapeutic expandable stent prosthesis for implantation in body lumens, e.g., vascular implantation and, more particularly, to a process for providing biostable elastomeric coatings on such stents which incorporate biologically active species having controlled release characteristics directly in the coating structure.

II. Related Art

In surgical or other related invasive medicinal procedures, the insertion and expansion of stent devices in

blood vessels, urinary tracts or other difficult to access places for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions has become a common form of long-term treatment. Typically, such prosthesis are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released to expand or be expanded in situ. These devices are generally designed as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

One type of self-expanding stent has a flexible tubular body formed of several individual flexible thread elements each of which extends in a helix configuration with the centerline of the body serving as a common axis. The elements are wound in a common direction, but are displaced axially relative to each other and meet, under crossing a like number of elements also so axially displaced, but having the opposite direction of winding. This configuration provides a resilient braided tubular structure which assumes stable dimensions upon relaxation. Axial tension produces elongation and corresponding diameter contraction that allows the stent to be mounted on a catheter device and conveyed through the vascular system as a narrow elongated device. Once tension is relaxed in situ, the device at least substantially reverts to its original shape. Prosthesis of the class including a braided flexible tubular body are illustrated and described in U.S.

Patents 4 655 771 and 4 954 126 to Wallsten and 5 061 275 to Wallsten et al.

Implanted stents have also been used to carry medicinal agents, such as thrombolytic agents. U.S. Patent 5 163 952 to Froix discloses a thermal memoried expanding plastic stent device which can be formulated to carry a medicinal agent by utilizing the material of the stent itself as an inert polymeric drug carrier. Pinchuk, in U.S. Patent 5 092 877, discloses a stent of a polymeric material which may be employed with a coating associated with the delivery of drugs. Other patents which are directed to devices of the class utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S. Patent 4 916 193, and MacGregor, U.S. Patent 4 994 071. Sahatjian in U.S. Patent No. 5 304 121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug; possible drugs include cell growth inhibitors and heparin. A further method of making a coated intravascular stent carrying a therapeutic material in which a polymer coating is dissolved in a solvent and the therapeutic material dispersed in the solvent and the solvent thereafter evaporated is described in Berg et al, U.S. Patent 5 464 650, issued November 5, 1995 and corresponding to European patent application 0 623 354 A1 published 09 November 1994.

An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design--A Systems Approach: Central Venous Catheters", 22nd International Society for the Advancement of Material and Process Engineering Technical Conference (1990) relates to

polymer/drug/membrane systems for releasing heparin. Those polymer/ drug/membrane systems require two distinct layers to function.

The above cross-referenced grandparent application supplies an approach that provides long-term drug release, i.e., over a period of days or even months, incorporated in a controlled-release system. The parent application and present invention provide a process for coating such stents including techniques that enable the initial burst effect of drug elation to be controlled and the drug release kinetic profile associated with long-term therapeutic effect to be modified.

Metal stents of like thickness and weave generally have better mechanical properties than polymeric stents. Metallic vascular stents braided of even relatively fine metal filament can provide a large amount of strength to resist inwardly directed circumferential pressure in blood vessels. In order for a polymer material to provide comparable strength characteristics, a much thicker-walled structure or heavier, denser filament weave is required. This, in turn, reduces the cross-sectional area available for flow through the stent and/or reduces the relative amount of open space available in the structure. In addition, when applicable, it is usually more difficult to load and deliver polymeric stents using vascular catheter delivery systems.

It will be noted, however, that while certain types of stents such as braided metal stents may be superior to others for some applications, the process of the present invention is not limited in that respect and may be used to coat a wide

variety of devices. The present invention also applies, for example, to the class of stents that are not self-expanding including those which can be expanded, for instance, with a balloon. Polymeric stents, of all kinds can be coated using the process. Thus, regardless of particular detailed embodiments the use of the invention is not considered or intended to be limited with respect either to stent design or materials of construction. Further, the present invention may be utilized with other types of implant prostheses.

Accordingly, it is a primary object of the present invention to provide a coating process for coating a stent to be used as a deployed stent prosthesis, the coating being capable of long-term delivery of biologically active materials.

Another object of the invention is to provide a process for coating a stent prosthesis using a biostable hydrophobic elastomer in which biologically active species are incorporated within a cured coating.

Still another object of the present invention is to provide a multi-layer coating in which the percentage of active material can vary from layer to layer.

A further object of the present invention is to control or modify aspects of the timed or time variable drug delivery from a stent coating by controlling average particle size in the biologically active species.

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

The present invention provides processes for producing a relatively thin layer of biostable elastomeric material in which an amount of biologically active material is dispersed as a coating on the surfaces of a deployable stent prosthesis. The preferred stent to be coated is a self-expanding, open-ended tubular stent prosthesis. Although other materials, including polymer materials, can be used, in the preferred embodiment, the tubular body is formed of an open braid of fine single or polyfilament metal wire which flexes without collapsing and readily axially deforms to an elongate shape for transluminal insertion via a vascular catheter. The stent resiliently attempts to resume predetermined stable dimensions upon relaxation in situ.

The coating is preferably applied as a mixture, solution or suspension of polymeric material and finely divided biologically active species dispersed in an organic vehicle or a solution or partial solution of such species in a solvent or vehicle for the polymer and/or biologically active species. For the purpose of this application, the term "finally divided" means any type or size of included material from dissolved molecules through suspensions, colloids and particulate mixtures. The active material is dispersed in a carrier material which may be the polymer, a solvent, or both. The coating is preferably applied as a plurality of relatively thin layers sequentially applied in relatively rapid sequence and is preferably applied with the stent in a radially expanded state. In some applications the coating may further be characterized as a composite initial tie coat or undercoat

and a composite topcoat. The coating thickness ratio of the topcoat to the undercoat may vary with the desired effect and/or the elution system. Typically these are of different formulations.

The coating may be applied by dipping or spraying using evaporative solvent materials of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thicknesses. The preferred process is predicated on reciprocally spray coating a rotating radially expanded stent employing an air brush device. The coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent but in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The coating is exposed to room temperature ventilation for a predetermined time (possibly one hour or more) for solvent vehicle evaporation. Thereafter the polymeric precuser material is cured at room temperature or elevated temperatures or the solvent evaporated away from the dissolved polymer as the case may be. Curing is defined as the process of converting the elastomeric or polymeric material into the finished or useful state by the application of heat and/or chemical agents which include physical-chemical charges. Where, for example, polyurethane thermoplastic elastomers are used, solvent evaporation can occur at room temperature rendering the polymeric material useful for controlled drug release without further curing. Non-limiting examples of

curing according to this definition include the application of heat and/or chemical agents and the evaporation of solvent which may induce physical and/or chemical changes.

The ventilation time and temperature for cure are determined by the particular polymer involved and particular drugs used. For example, silicone or polysiloxane materials (such as polydimethylsiloxane) have been used successfully. These materials are applied as pre-polymer in the coating composition and must thereafter be cured. The preferred species have a relatively low cure temperatures and are known as a room temperature vulcanizable (RTV) materials. Some polydimethylsiloxane materials can be cured, for example, by exposure to air at about 90°C for a period of time such as 16 hours. A curing step may be implemented both after application of a certain number of lower undercoat layers and the topcoat layers or a single curing step used after coating is completed.

The coated stents may thereafter be subjected to a postcure sterilization process which includes an inert gas plasma treatment, and then exposure to gamma radiation, electron beam, ethylene oxide (ETO) or steam sterilization may also be employed.

In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to about 20-50mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon

gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to about 100 - 450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After the argon plasma pretreatment, the coated and cured stents are subjected to gamma radiation sterilization nominally at 2.5-3.5 Mrad. The stents enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status. It has been found that constrained stents subjected to gamma sterilization without utilizing the argon plasma pretreatment lose resiliency and do not recover at a sufficient or appropriate rate.

The elastomeric material that forms a major constituent of the stent coating should possess certain properties. It is preferably a suitable hydrophobic biostable elastomeric material which does not degrade and which minimizes tissue rejection and tissue inflammation and one which will undergo encapsulation by tissue adjacent to the stent implantation site. Polymers suitable for such coatings include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes (including polycarbonate urethanes), thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and polyamide elastomers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention.

Agents suitable for incorporation include antithrobotics, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, antinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, antibiotics growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

The preferred materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Further details concerning the fabrication and details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Patents 4 655 771 and 4 954 126 to Wallsten and 5 061 275 to Wallsten et al. To the extent additional information contained in the above-referenced patents is necessary for an understanding of the present invention, they are deemed incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic

materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

For the purposes of this specification, "elution" is defined as any process of release that involves extraction or release by direct contact of the material with bodily fluids through the interparticle paths connected with the exterior of the coating. "Transport" or "diffusion" are defined to include a mechanism of release in which a material released traverses through another material.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution (layer to layer) of bioactive materials, the mixing method, the amount of bioactive material, the combination of different matrix polymer materials at different layers, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, during the curing process, determines the amount of crosslinking and so the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as

heparin, a crosslink structure of greater density will increase release time and reduce burst effect.

Additionally, with eluting materials such as heparin, release kinetics, particularly initial drug release rate, can be affected by varying the average dispersed particle size. The observed initial release rate or burst effect may be substantially reduced by using smaller particles, particularly if the particle size is controlled to be less than about 15 microns and the effect is even more significant in the particle size range of ≤ 10 microns, especially when the coating thickness is not more than about 50μm and drug loading is about 25-45 weight percent.

It will also be appreciated that an unmedicated silicone thin top layer provides an advantage over drug containing top coat. Its surface has a limited porosity and is generally smooth, which may be less thrombogeneous and may reduce the chance to develop calcification, which occurs most often on the porous surface.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIGURE 1 is a schematic flow diagram illustrating the steps of the process of the invention;

FIGURE 2 represents a release profile for a multi-layer system showing the percentage of heparin released over a two-week period;

FIGURE 3 represents a release profile for a multi-layer system showing the relative release rate of heparin over a two-week period;

FIGURE 4 illustrates a profile of release kinetics for different drug loadings at similar coating thicknesses illustrating the release of heparin over a two-week period;

FIGURE 5 illustrates drug elution kinetics at a given loading of heparin over a two-week period at different coating thicknesses;

FIGURE 6 illustrates the release kinetics in a coating having a given tie-layer thickness for different top coat thicknesses in which the percentage heparin in the tie coat and top coats are kept constant;

FIGURE 7 illustrates the release kinetics of several coatings having an average coating thickness of 25 microns and a heparin loading of 37.5% but using four different average particle sizes;

FIGURES 8-11 are photomicrographs of coated stent fragments for the coatings of FIGURE 7 having a corresponding average particle size of 4 microns, 17 microns, 22 microns and 30 microns, respectively.

DETAILED DESCRIPTION

According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in Figure 1. The coating solutions or suspensions

are prepared at 10 as will be described later. The desired amount of crosslinking agent is added to the suspension/solution as at 12 and material is then agitated or stirred to produce a homogenous coating composition at 14 which is thereafter transferred to an application container or device which may be a container for spray painting at 16. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

General Preparation of Heparin Coating Composition

Silicone was obtained as a polymer precursor in solvent (xylene) mixture. For example, a 35% solid silicone weight content in xylene was procured from Applied Silicone, Part #40,000. First, the silicone-xylene mixture was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated amounts of finely divided heparin (2-6 microns) were added into the silicone, then tetrahydrofuron (THF) HPCL grade (Aldrich or EM) was added. For a 37.5% heparin coating, for example: $W_{silicone}$ = 5 g; solid percent = 35%; W_{hep} = 5 x 0.35x .375/(0.625) = 1.05 g. The amount of THF needed (44 ml) in the coating solution was calculated by using the equation $W_{silicone\ solid}/V_{THF}$ = 0.04 for a 37.5% heparin coating solution). Finally, the manufacturer crosslinker solution was added by using Pasteur P-pipet. The amount of crosslinker added was formed to effect the release rate profile. Typically, five drops of crosslinker solution were added for each five grams of silicone-xylene mixture. The crosslinker may be any suitable and compatible agent including platinum and peroxide based materials. The solution

was stirred by using the stirring rod until the suspension was homogenous and milk-like. The coating solution was then transferred into a paint jar in condition for application by air brush.

General Preparation of Dexamethasone Coating Composition

Silicone (35% solution as above) was weighed into a beaker on a Metler balance. The weight of dexamethasone free alcohol or acetate form was calculated by silicone weight multiplied by 0.35 and the desired percentage of dexamethasone (1 to 40%) and the required amount was then weighed. Example: $W_{silicone}$ = 5 g; for a 10% dexamethasone coating, W_{dex} = 5 x 0.35 x 0.1/0.9 = 0.194 g and THF needed in the coating solution calculated. $W_{silicone\ solid}/V_{THF}$ = 0.06 for a 10% dexamethasone coating solution. Example: $W_{silicone}$ = 5 g; V_{THF} = 5 x 0.35/0.06 = 29 ml. The dexamethasone was weighed in a beaker on an analytical balance and half the total amount of THF was added. The solution was stirred well to ensure full dissolution of the dexamethasone. The stirred DEX-THF solution was then transferred to the silicone container. The beaker was washed with the remaining THF and this was transferred to the silicone container. The crosslinker was added by using a Pasteur pipet. Typically, five drops of crosslinker were used for five grams of silicone.

The application of the coating material to the stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, typically a paint jar attached to an air

brush, such as a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0-160 psi). Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately 15-25 psi and the nozzle condition checked by depressing the trigger.

Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the desired coating speed, nominally about 40 rpm.

With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2-4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating layers did and will vary with the particular application. For example, for a coating level of 3-4 mg of heparin per cm^2 of projected area, 20 cycles of coating

application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30-50 rpm and with a spray nozzle flow rate in the range of 4-10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Several applied layers make up what is called the tie layer as at 18 and thereafter additional upper layers, which may be of a different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, are applied as the top layer as at 20. The application of the top layer follows the same coating procedure as the tie layer with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by modifying the speed of rotation of the stent and the spraying conditions. Generally, the total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

As shown at 22 in Figure 1, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing

process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50°C) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90°C or higher for approximately 16 hours. The temperature may be raised to as high as 150°C for dexamethasone containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers, and biologically active species.

Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at 24 is first applied to the coated, cured stent.

The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, CA). The system is equipped with a reactor chamber and

RF solid-state generator operating at 13.56 mHz and from 0-500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 16.75 inches (42.55 cm) by 13.5 inches (34.3 cm) by 17.5 inches (44.45 cm) in depth.

In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20-50mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to 100 - 450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After this, as shown at 26, the stents are exposed to gamma sterilization at 2.5-3.5 Mrad. The radiation may be carried out with the stent in either the radially non-constrained status - or in the radially constrained status.

With respect to the anticoagulant material heparin, the percentage in the tie layer is nominally from about 20-50% and that of the top layer from about 0-30% active material. The coating thickness ratio of the top layer to the tie layer varies from about 1:10 to 1:2 and is preferably in the range of from about 1:6 to 1:3.

Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subcute thrombosis.

Figure 4 depicts the general effect of drug loading for coatings of similar thickness. The initial elution rate increases with the drug loading as shown in Figure 5. The release rate also increases with the thickness of the coating at the same loading but tends to be inversely proportional to the thickness of the top layer as shown by the same drug loading and similar tie-coat thickness in Figure 6.

The effect of average particle size is depicted in the FIGURES 7-11 in which coating layers with an average coating thickness of about 25 microns (μm), prepared and sterilized as above, were provided with dispersed heparin particles (to 37.5% heparin) of several different average particle sizes. FIGURE 7 shows plots of elution kinetics for four different sizes of embedded heparin particles. The release took place in phosphate buffer (pH 7.4) at 37°C. The release rate using smaller, particularly 4-6μm average sized particles noticeably reduces the initial rate or burst effect and thereafter the elution rate decreases more slowly with time. Average particle sizes above about 15 μm result in initial release

rates approaching bolus elution. This, of course, is less desirable, both from the standpoint of being an unnecessary initial excess and for prematurely depleting the coating of deserved drug material.

In addition, as shown in the photomicrographs of FIGURES 8-11, as the average particle size increases, the morphology of the coating surface also changes. Coatings containing larger particles (FIGURES 9-11) have very rough and irregular surface characteristics. These surface irregularities may be more thrombogenic or exhibit an increased tendency to cause embolization when the corresponding stent is implanted in a blood vessel.

Accordingly, it has been found that the average particle size should generally be controlled below about 15 μm to reduce the burst effect and preferably should be ≤ about 10 μm for best results. The 4-6μm size worked quite successfully in the laboratory. However, it should be noted that larger particle size can also be advantageously used, for instance, when the drug load is low, such as below 25 weight percent. Elution kinetics can be adjusted by a combination of changing the particle size and changing the load or concentration of the dispersed drug material.

What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be modified to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For

example, antiproliferation drugs may be combined in the undercoat and anti-thrombotic drugs in the topcoat layer. In this manner, the anti-thrombotic drugs, for example, heparin, will elute first followed by antiproliferation drugs, e.g. dexamethasone, to better enable safe encapsulation of the implanted stent.

The heparin concentration measurement were made utilizing a standard curve prepared by complexing azure A dye with dilute solutions of heparin. Sixteen standards were used to compile the standard curve in a well-known manner.

For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at approximately 37°C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

As stated above, while the allowable loading of the elastomeric material with heparin may vary, in the case of silicone materials heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an

important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the above examples depict coatings having two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of

silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which result in a great deal of flexibility with respect to controlling the release of biologically active materials with regard to an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15 microns in thickness. The total number of sprayed layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness of the coating can also vary widely, but can generally be from about 10 to 200 microns.

Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

CLAIMS

We claim:

1. A method of coating an implantable prosthesis with a layer comprising an hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom comprising the steps of:

(a) applying a formulation containing polymeric material in solvent mixture and an amount of finely divided biologically active species;

(b) curing said polymeric material; and

(c) wherein the average particle size of the finely divided biological species in said coating formulation is selected to affect delivery kinetics.

2. The method of claim 1 wherein the elastomeric material is selected from the group consisting of silicones, polyurethanes, polyamide elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and combinations thereof.

3. The method of claim 1 wherein the biologically active material has an average particle size ≤ about 15 μm.

4. The method of claim 2 wherein the biologically active material includes heparin.

5. The method of claim 4 wherein the layer comprises about 25-45 weight percent biologically active material.

6. The method of claim 1 wherein the biologically active material has an average particle size ≤ 10 μm.

7. The method of claim 6 wherein the biologically active material includes heparin.

8. A method of controlling the kinetics of an eluting (biologically active) particulate material incorporated in a polymeric coating in an implantable prosthesis comprising the step of controlling the average particle size below a designated maximum size.

9. The method of claim 7 wherein said biologically active material is heparin and the average particle size is ≤ about 15 μm.

10. The method of claim 9 wherein the layer comprises about 25-45 weight percent biologically active material.

11. A method of controlling the kinetics of an eluting (biologically active) particulate material incorporated in a polymer coating in an implantable prosthesis comprising the steps of selecting an average particle size and a drug load to produce desired delivery kinetics.

12. The method of claim 11 further comprising the steps of selecting an average particle size and a drug load to produce a substantially smooth surface on the prosthesis.

13. The method of claim 11 wherein the layer comprises about 25-45 weight percent biologically active material.

14. The method of claim 13 wherein said biologically active material is heparin and the average particle size is ≤ about 15 μm.

15. A coated implantable prosthesis having an external surface covered with a conformal coating comprising a hydrophobic elastomeric material incorporating an amount of biologically active material in particulate form dispersed therein for timed delivery therefrom wherein the delivery kinetics thereof is controlled at least in part by variations in parameters selected from the group consisting of average particle size and concentration of dispersed material in said coating or a combination thereof.

16. The device of claim 15 wherein the delivery kinetics are controlled by variations in particle size.

17. The device of claim 15 wherein the elastomeric material is selected from the group consisting of silicones, polyurethanes, polyamide elastomers, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and combinations thereof.

18. The device of claim 15 wherein the biologically active material has an average particle size ≤ about 15 μm.

19. The device of claim 18 wherein the biologically active material includes heparin.

20. The device of claim 15 wherein the layer comprises about 25-45 weight percent biologically active material.

21. The device of claim 15 wherein the biologically active material has an average particle size ≤ 10 μm.

22. The device of claim 21 wherein the biologically active material includes heparin.

23. The device of claim 15 wherein the layer comprises about 25-45 weight percent biologically active material and wherein the biologically active material is heparin having an average particle size ≤ 10 microns.

DRUG RELEASE STENT COATING PROCESS

BACKGROUND OF THE INVENTION

A method of coating implantable open lattice metallic stent prosthesis is disclosed which includes sequentially applying a plurality of relatively thin outer layers of a coating composition comprising a solvent mixture of uncured polymeric silicone material and crosslinker and finely divided biologically active species, possibly of controlled average particle size, to form a coating on each stent surface. The coatings are cured in situ and the coated, cured prosthesis are sterilized in a step that includes preferred pretreatment with argon gas plasma and exposure to gamma radiation electron beam, ethylene oxide, steam.

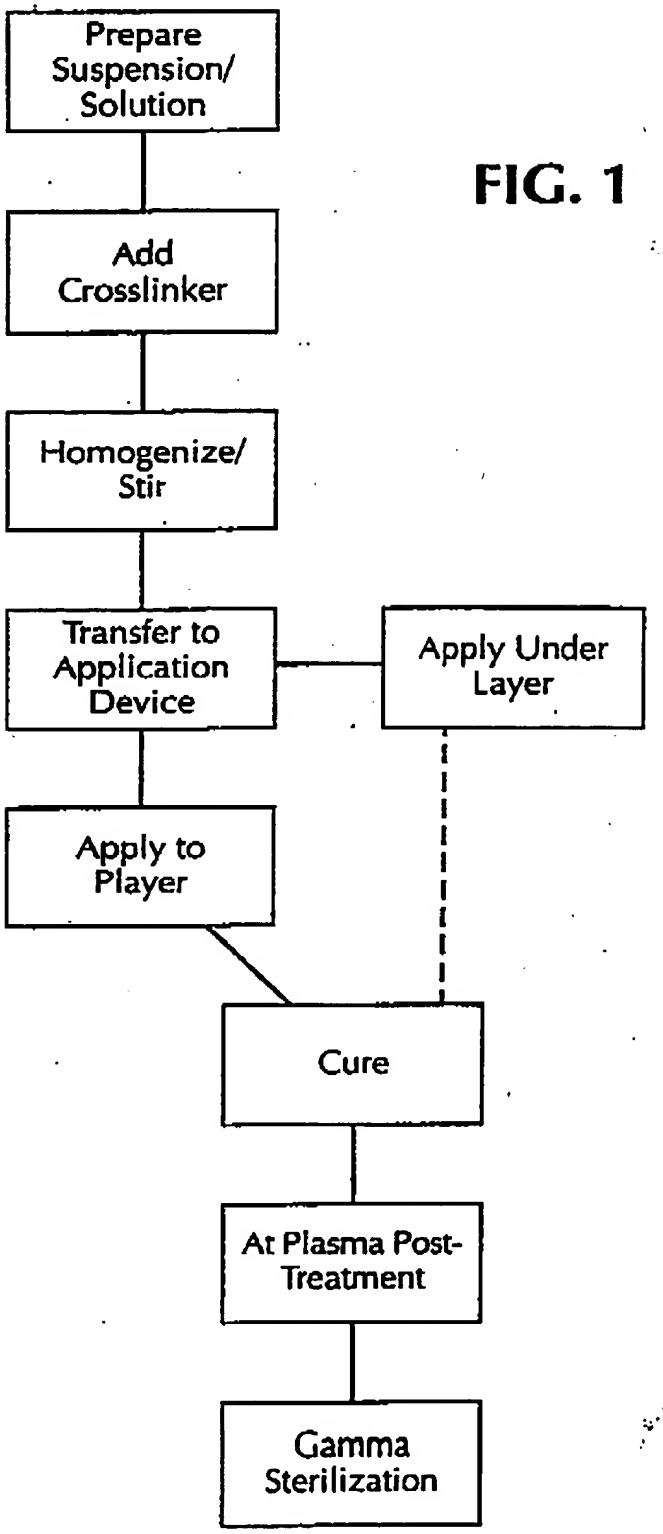

Prepare Suspension/ Solution
Add Crosslinker
Homogenize/ Stir
Transfer to Application Device
Apply Under Layer
Apply to Player
Cure
At Plasma Post-Treatment
Gamma Sterilization

FIG. 1

FIG. 2

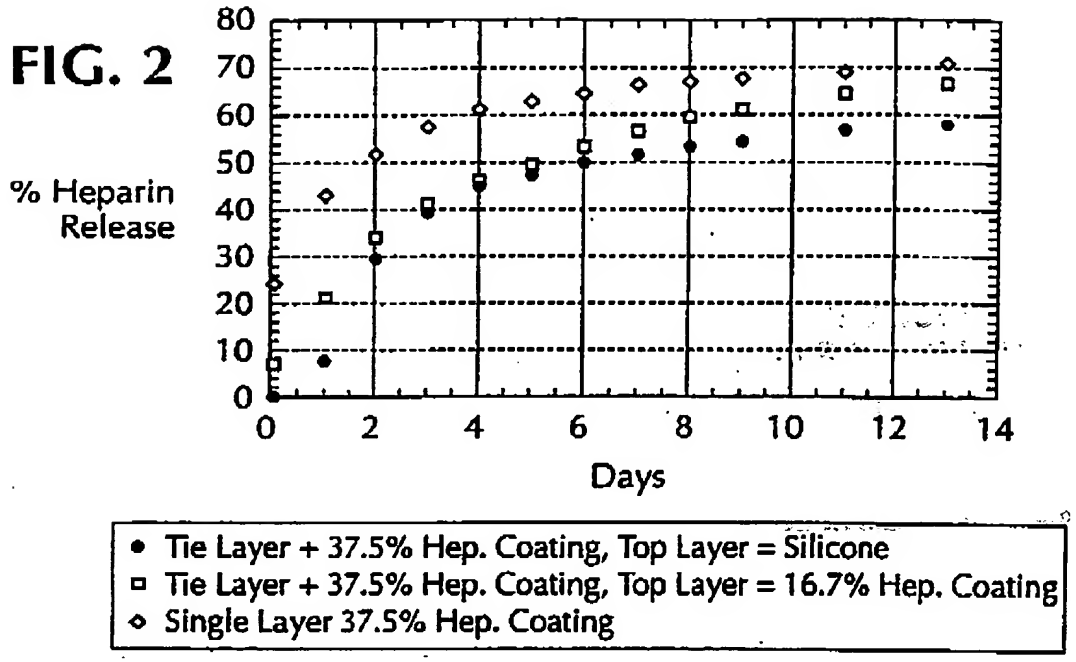

% Heparin Release
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
Days
Tie Layer + 37.5% Hep. Coating, Top Layer = Silicone
Tie Layer + 37.5% Hep. Coating, Top Layer = 16.7% Hep. Coating
Single Layer 37.5% Hep. Coating

FIG. 3

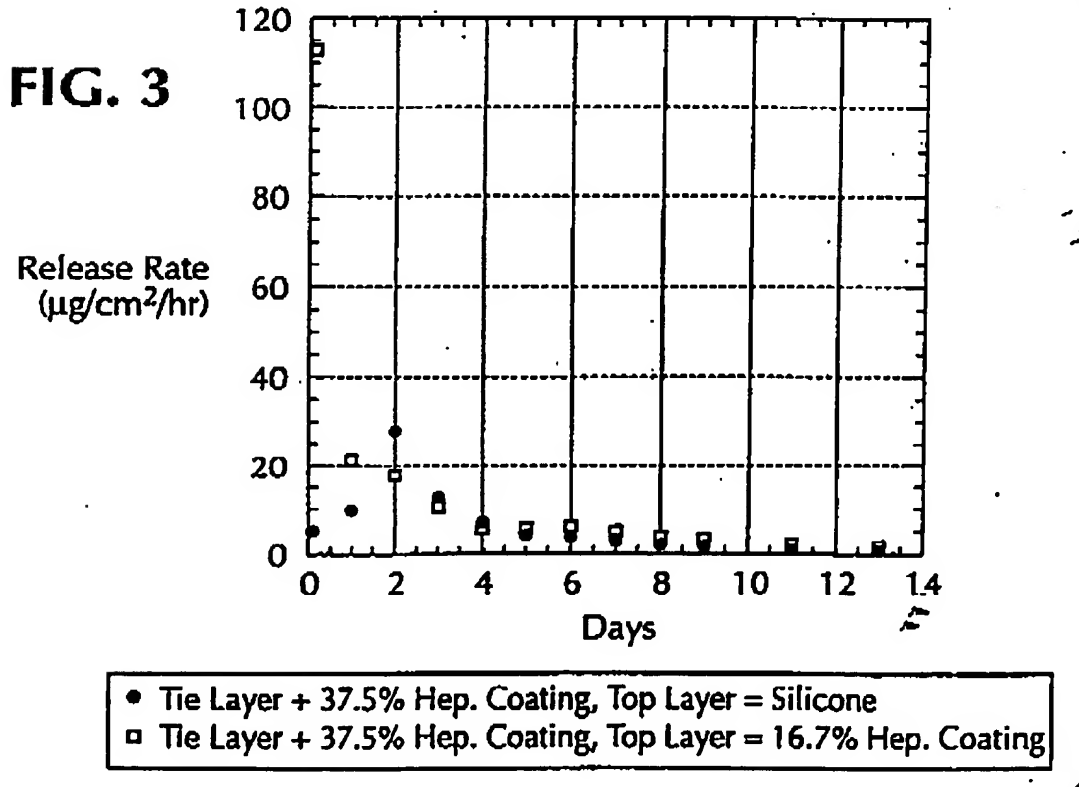

Release Rate (µg/cm²/hr)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Days
Tie Layer + 37.5% Hep. Coating, Top Layer = Silicone
Tie Layer + 37.5% Hep. Coating, Top Layer = 16.7% Hep. Coating

FIG. 4

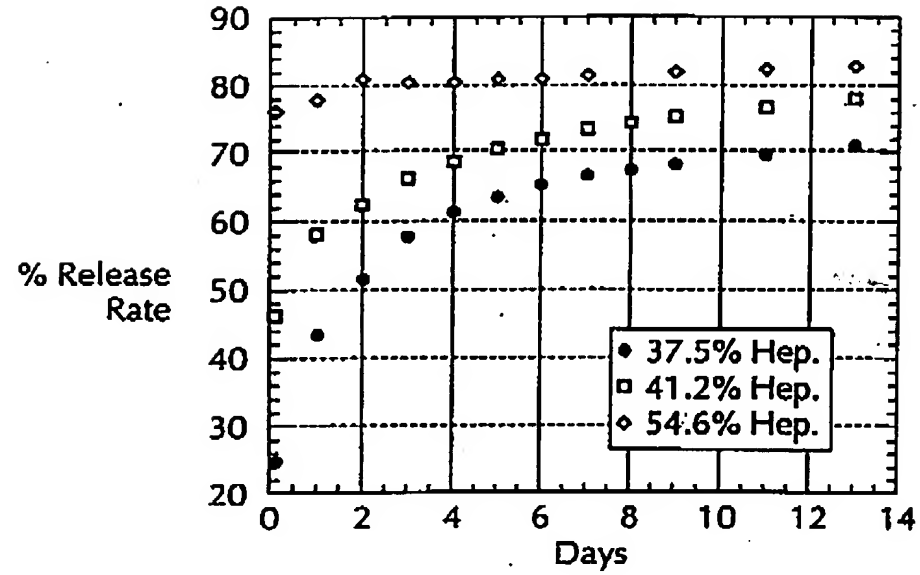


FIG. 5

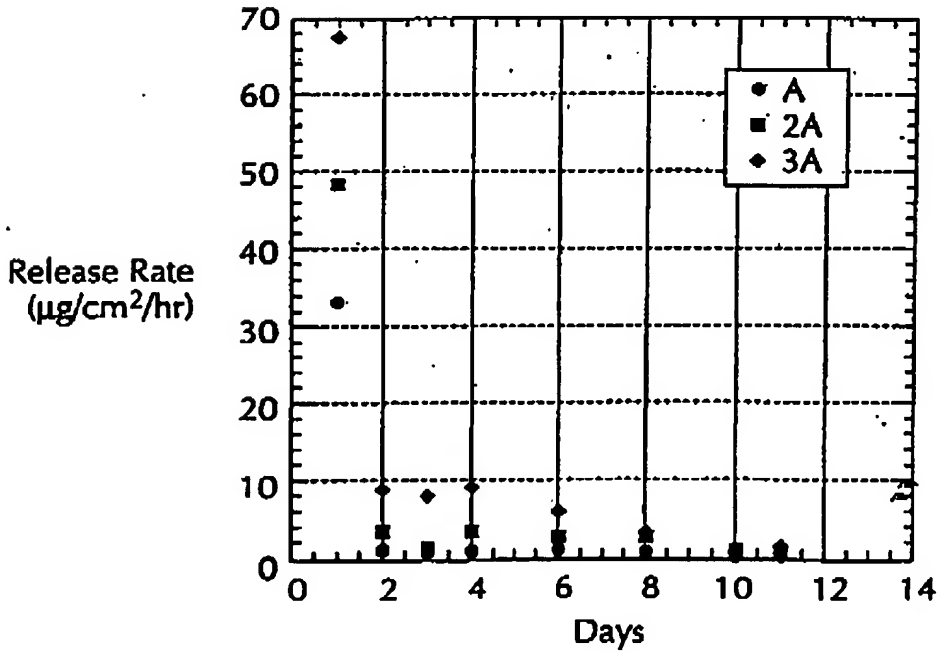
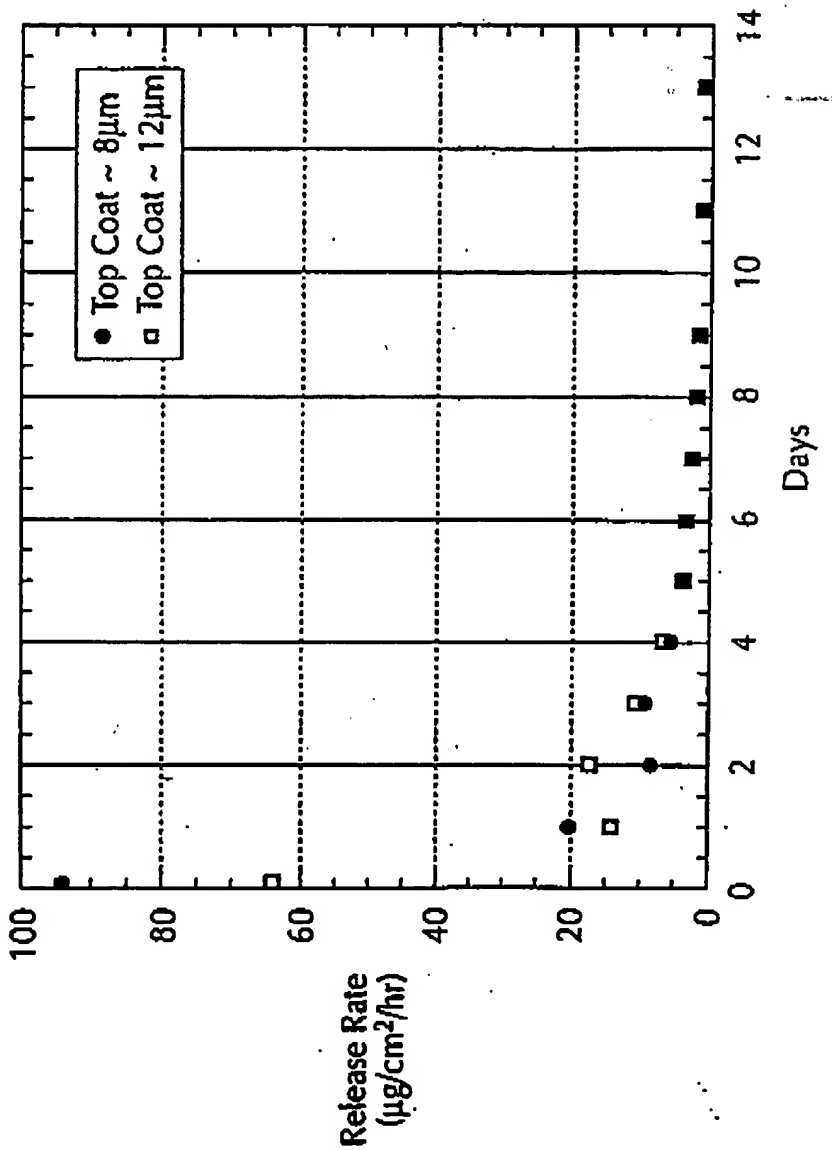


FIG. 6



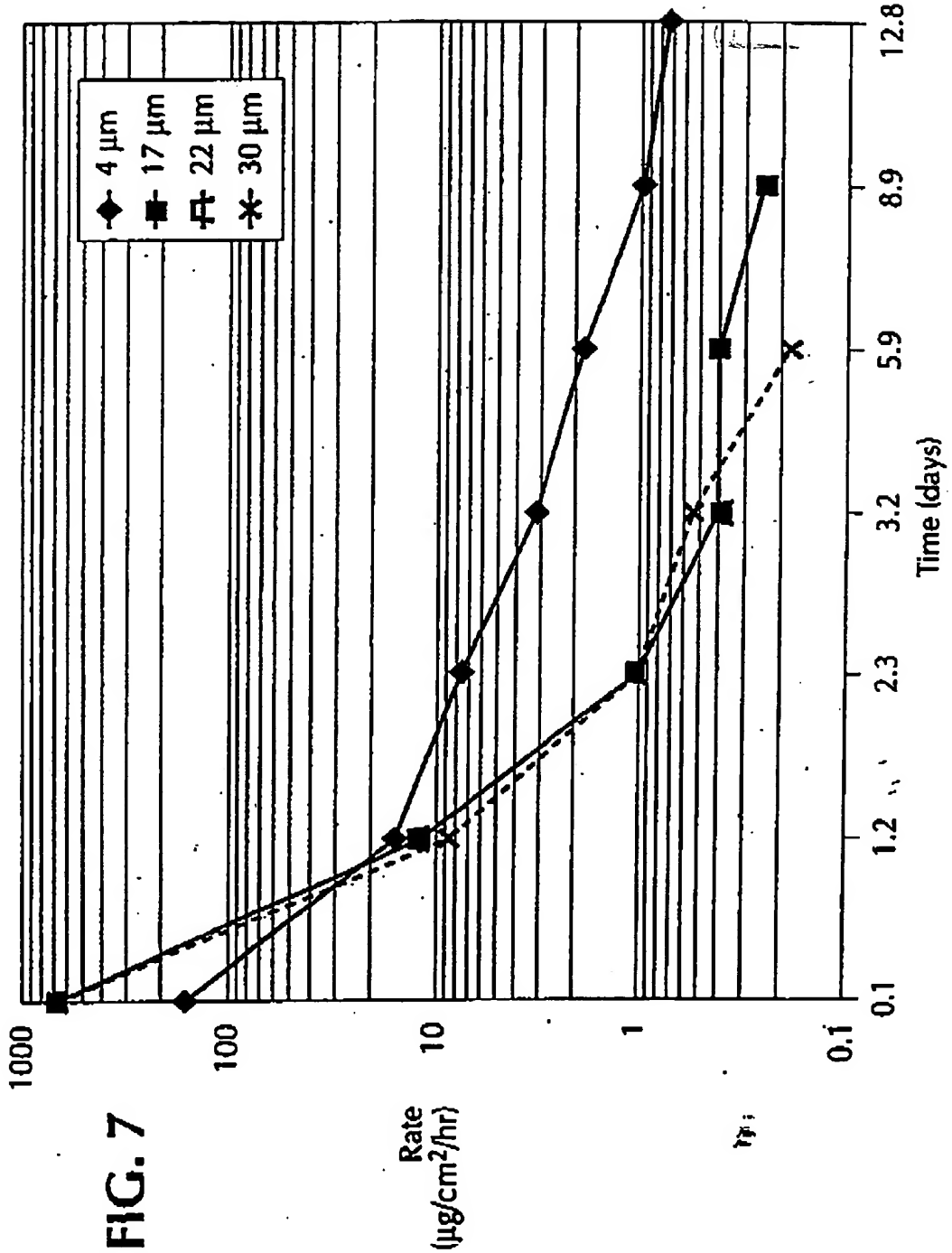

4 µm
17 µm
22 µm
30 µm
1000
100
10
1
0.1
Rate (µg/cm²/hr)
0.1
1.2
2.3
3.2
5.9
8.9
12.8
Time (days)

FIG. 7

FIG. 8

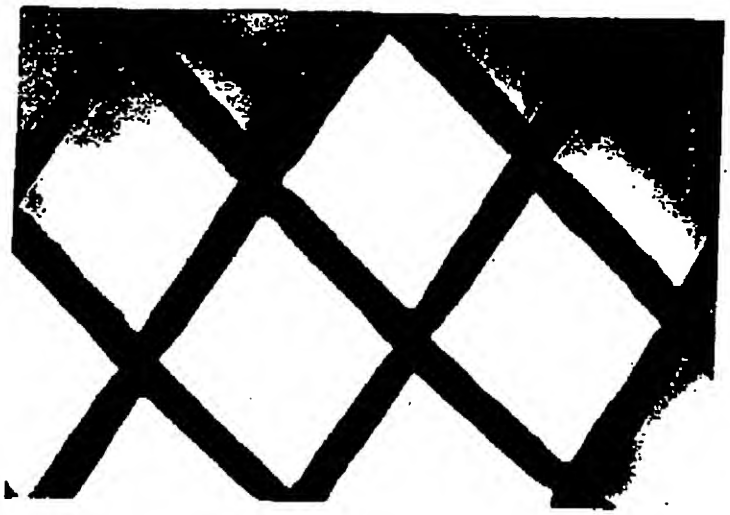
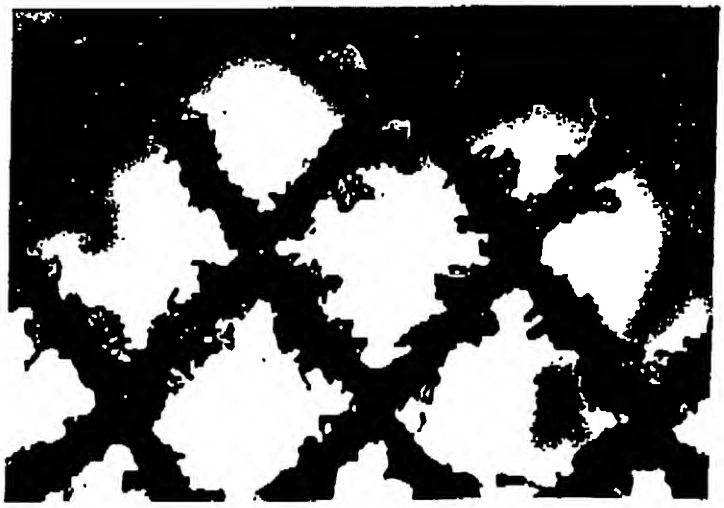


FIG. 9

FIG. 10

FIG. 11



Appendix B
U.S. Patent Application No. 08/424,884

DRUG RELEASE COATED STENT

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to elastic, self-expanding stent prostheses for lumen, e.g., vascular, implantation and, more particularly, to the provision of biostable elastomeric coatings on such stents which incorporate elutable or diffusible biologically active species for controlled release directly in the coating structure.

II. Related Art

In surgical or other related invasive medicinal procedures, the insertion and expansion of stent devices in blood vessels, urinary tracts or other difficult to access places for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions have become a common form of long-term treatment. Typically, such prostheses are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released and expanded in situ. These devices are designed primarily as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

Stent devices of the self-expanding tubular type for transluminal implantation, then, are generally known. One type of such device includes a flexible tubular body which is composed of several individual flexible thread elements each of which extends

in a helix configuration with the centerline of the body serving as a common axis. A plurality of elements having the same direction of winding but which are displaced axially relative to each other are provided which meet under crossing a like number of elements also so axially displaced but having the opposite direction of winding. This configuration provides a sort of braided tubular structure which assumes a stable dedicated diameter upon the relaxation but which can be reduced as for insertion by the application of axial tension which, in turn, produces elongation of the body with a corresponding diameter contraction that allows the stent to be conducted through the vascular system as a narrow elongated device and thereafter allowed to expand upon relaxation at the location of interest. Prostheses of the class including a braided flexible tubular body are illustrated and described in U.S. Patents 4 655 771 and 4 954 126 to Wallsten and 5 061 275 to Wallsten et al.

The general idea of utilizing implanted stents to carry medicinal agents, such as thrombolytic agents, also have been devised. U.S. Patent 5 163 952 to Froix discloses a thermal memoried expanding plastic stent device which can be formulated to carry a medicinal agent by utilizing the material of the stent itself as an inert polymeric drug carrier. Pinchuk, in U.S. Patent 5 092 877, discloses a stent of a polymeric material which may be employed with a coating associated with the delivery of drugs. Other patents which are directed to devices of the class utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S.

Patent 4 916 193, and MacGregor, U.S. Patent 4 994 071. A patent to Sahatjian, Patent No. 5 304 121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug in which possible drugs include cell growth inhibitors and heparin. A further method of making a coated intravascular stent carrying a therapeutic material in which a polymer coating is dissolved in a solvent and the therapeutic material dispersed in the solvent and the solvent thereafter evaporated is described in European patent application 0 623 354 A1 published 09 November 1994.

An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design--A Systems Approach: Central Venous Catheters", 22nd International Society for the Advancement of Material and Process Engineering Technical Conference (1990) discloses surfactant-heparin complexes to be used as controlled release heparin coatings. Those polymer/drug/membrane systems require two distinct layers of function.

While many attempts have been made to incorporate drug delivery in conjunction with long-term catheter or implanted stent placement, for example, the associated release time has been generally, relatively short, measured in hours and days, and success has been limited. There remains a need for a comprehensive approach that provides long-term drug release, i.e., over a period of weeks or months, incorporated in a controlled-release system. In addition, there is a further need with respect to incorporating a drug release coating on a metallic stent. Polymeric stents, although effective, cannot equal the mechanical properties of metal

stents of a like thickness. For example, in keeping a vessel open, a metallic stent is superior because stents braided of relatively fine metal can provide a good deal of strength to resist circumferential pressure. In order for a polymer material to provide the same strength characteristics, a much thicker-walled structure or heavier, denser filament weave is required. This, in turn, reduces the area available for flow through the stent and/or reduces the amount of porosity available in the stent. In addition, when applicable, it is more difficult to load such a stent onto catheter delivery systems for conveyance through the vascular system of the patient to the site of interest.

Accordingly, it is a primary object of the present invention to provide a coating in a deployed stent prosthesis capable of long-term delivery of biologically active materials.

Another object of the invention is to provide a coating on a deployed stent prosthesis of optimal mechanical properties with minimal surface area for long-term delivery of biologically active therapeutic materials.

Still another object of the present invention is to provide a coating on a deployed stent prosthesis using a biostable hydrophobic elastomer in which the biologically active species is incorporated within the coating.

A still further object of the invention is to provide a deployed stent prosthesis of a siloxane polymer containing crystals of heparin for dissolution via interconnected particle interstices.

A yet still further object of the present invention is to provide a braided metallic deployed stent prosthesis having a coating of a siloxane polymer material containing an amount of dissolved and/or finely divided dexamethasone.

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

Many of the limitations of prior art implanted prolonged drug delivery systems associated with deployed stent prostheses are overcome by the provision of a relatively thin overlayer of biostable elastomeric material in which an amount of biologically active material is dispersed as a coating on the surfaces of the stent. The preferred stent is a self-expanding, open-ended tubular stent prosthesis, with a thin porous flexible elastic sidewall. Although other materials can be used including polymer materials, in the preferred embodiment, the tubular body is formed of an open braid of fine single or polyfilament wire which flexes without collapsing and is axially deformable for insertion using a catheter or other such device but which resumes a predetermined stable diameter and length upon relaxation.

The coating layer is preferably applied as a mixture of polymeric precursor and finely divided biologically active species or a solution or partial solution of such species in the polymer solvent or vehicle which is thereafter cured in situ. The coating may be applied by dipping or spraying using evaporative solvent

materials of relatively high vapor pressure to produce the desired viscosity and coating thickness. The coating further is one which adheringly conforms to the surface of the filaments of the open structure of the stent so that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The elastomeric material that forms a major constituent of the stent coating should possess certain properties. It is preferably a suitable hydrophobic biostable elastomeric material which does not degrade and which minimizes tissue rejection and tissue inflammation and one which will undergo encapsulation by tissue adjacent the stent implantation site. Polymers suitable for such coatings include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention.

Agents suitable for incorporation include antithrobotics, anticoagulants, antiplatelet agents, thorombolytics, antiproliferatives, antinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation

(e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

The preferred materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Further details concerning the fabrication and details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Patents 4 655 771 and 4 954 126 to Wallsten and 5 061 275 to Wallsten et al. To the extent additional information contained in the above-referenced patents is necessary for an understanding of the present invention, they are deemed incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution of bioactive materials, the mixing method, the amount of bioactive material, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, after the curing process, determines the amount of crosslinking and so the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a denser crosslink structure will result in a longer release time and small burst effect.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIGURES 1 and 1A depict greatly enlarged views of a fragment of a medical stent for use with the coating of the invention;

FIGURES 2A and 2B depict a view of a stent section as pictured in Figures 1 and 1A as stretched or elongated for insertion;

FIGURE 3 is a light microscopic photograph of a typical uncoated stent structure configuration (20X);

FIGURE 4A is a scanning electron microscope photograph (SEM) of a heparin containing poly siloxane coating on a stent in accordance with the invention (X20) after release of heparin into buffer for 49 days;

FIGURE 4B is a higher powered scanning electron microscopic photograph (SEM) of the coating of Figure 4A (X600);

FIGURE 5A is another scanning electron microscopic photograph (SEM) of a different stent coated with coating as produced with heparin incorporated into the polysiloxane (X20);

FIGURE 5B is an enlarged scanning electron microscopic photograph (SEM) of the coating of Figure 5B (X600);

FIGURE 6A is a light microscopic picture (X17.5) of a histologic cross-section of a silicone/heparin coated stent implanted in a swine coronary for 1 day;

FIGURE 6B depicts a pair of coated filaments of the stent of Figure 6A (X140) showing the open porous structure of the silicone;

FIGURE 7A is a scanning electron microscope photograph (SEM) that depicts a polysiloxane coating containing 5% dexamethasone (X600);

FIGURE 7B depicts the coating of Figure 7A (SEM X600) after dexamethasone release in polyethylene glycol (PEG 400/H_2O) for three months;

FIGURE 8 is a plot showing the total percent heparin released over 90 days from a coated stent in which the coated layer is 50% heparin (based on the total weight of the coating) in a silicone polymer matrix; release took place in phosphoric buffer (pH=7.4) at 37°C; and

FIGURE 9 is a plot of the total percent dexamethasone released over -100 days for two percentages of dexamethasone in silicon

coated stents; release took place in polyethylene glycol (PEG), MW=400 (PEG 400/H_2O, 40/60, vol/vol) at 37°C.

DETAILED DESCRIPTION

A type of stent device of one class designed to be utilized in combination with coatings in the present invention is shown diagrammatically in a side view and an end view, respectively contained in Figures 1A and 1B. Figure 1A shows a broken section of a generally cylindrical tubular body 10 having a mantle surface formed by a number of individual thread elements 12, 14 and 13, 15, etc. of these elements, elements 12, 14, etc. extend generally in an helix configuration axially displaced in relation to each other but having center line 16 of the body 10 as a common axis. The other elements 13, 15, likewise axially displaced, extend in helix configuration in the opposite direction, the elements extending in the two directions crossing each other in the manner indicated in Figure 1A. A tubular member so concerned and so constructed can be designed to be any convenient diameter, it being remembered that the larger the desired diameter, the larger the number of filaments of a given wire diameter (gauge) having common composition and prior treatment required to produce a given radial compliance.

The braided structure further characteristically readily elongates upon application of tension to the ends axially displacing them relative to each other along center line 16 and correspondingly reducing the diameter of the device. This is illustrated in Figures 2A and 2B in which a segment of the device 10 of Figures 1A and 1B has been elongated by moving the ends 18

and 20 away from each other in the direction of the arrows. Upon the release of the tension on the ends, the structure 10, if otherwise unrestricted, will reassume the relaxed or unloaded configuration of Figures 1A and 1B.

The elongation/resumption characteristic flexibility of the stent device enables it to be slipped or threaded over a carrying device while elongated for transportation through the vascular or other relevant internal luminal system of a patient to the site of interest where it can be axially compressed and thereby released from the carrying mechanism, often a vascular catheter device. At the site of interest, it assumes an expanded condition held in place by mechanical/frictional pressure between the stent and the lumen wall against which it expands.

The elongation, loading, transport and deployment of such stents is well known and need not be further detailed here. It is important, however, to note that when one contemplates coatings for such a stent in the manner of the present invention, an important consideration resides in the need to utilize a coating material having elastic properties compatible with the elastic deforming properties residing in the stent that it coats. The material of the stent should be rigid and elastic but not plastically deformable as used. As stated above, the preferred materials for fabricating the metallic braided stent include stainless steel, tantalum, titanium alloys including nitinol and certain cobalt-chromium alloys. The diameter of the filaments may vary but for

vascular devices, up to about 10 mm in diameter is preferable with the range 0.01 to 0.05 mm.

Drug release surface coatings on stents in accordance with the present invention can release drugs over a period of time from days to months and can be used, for example, to inhibit thrombus formation, inhibit smooth muscle cell migration and proliferation, inhibit hyperplasia and restenosis, and encourage the formation of health neointimal tissue including endothelial cell regeneration. As such, they can be used for chronic patency after an angioplasty or stent placement. It is further anticipated that the need for a second angioplasty procedure may be obviated in a significant percentage of patients in which a repeat procedure would otherwise be necessary. A major obstacle to the success of the implant of such stents, of course, has been the occurrence of thrombosis in certain arterial applications such as in coronary stenting. Of course, antiproliferative applications would include not only cardiovascular but any tubular vessel that stents are placed including urologic, pulmonary and gastro-intestinal.

Various combinations of polymer coating materials can be coordinated with the braided stent and the biologically active agent of interest to produce a combination which is compatible at the implant site of interest and controls the release of the biologically active species over a desired time period. Preferred coating polymers include silicones (poly siloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate

copolymers, polyolefin rubbers, EPDM rubbers, and combinations thereof.

Specific embodiments of the present invention include those designed to elute heparin to prevent thrombosis over a period of weeks or months or to allow the diffusion or transport of dexamethasone to inhibit fibromuscular proliferation over a like period of time. Of course, other therapeutic substances and combinations of substances are also contemplated. The invention may be implanted in a mammalian system, such as in a human body.

The heparin elution system is preferably fabricated by taking finely ground heparin crystal, preferably ground to an average particle size of less than 10 microns, and blending it into a liquid, uncured poly siloxane/solvent material in which the blend (poly siloxane plus heparin) contains from less than 10% to as high as 80% heparin by weight with respect to the total weight of the material and typically the layer is between 10% and 45% heparin.

This material is solvent diluted and utilized to coat a metallic braided stent, which may be braided cobalt chromium alloy wire, in a manner which applies a thin, uniform coating (typically between 20 and 200 microns in thickness)of the heparin/polymer mixture on the surfaces of the stent. The polymer is then heat cured, or cured using low temperature thermal initiators (<100°C) in a room temperature vulcanization (RTV) process in situ on the stent evaporating solvent, typically tetrahydrofuran (THF) with the heparin forming interparticle paths in the silicone sufficiently interconnected to allow slow but substantially complete subsequent

elution. The ultrafine particle size utilized allows the average pore size to be very small such that elution may take place over weeks or even months.

A coating containing dexamethasone is produced in a somewhat different manner. A poly siloxane material is also the preferred polymeric material. Nominally an amount equal to 0.4% to about 45% of the total weight of the layer of dexamethasone is used.

The dexamethasone drug is dissolved in a solvent, e.g., THF first. The solution is then blended into liquid uncured poly siloxane/solvent (xylene, THF, etc.) vehicle precursor material. Since the dexamethasone is also soluble in the solvent for the polysiloxane, it dissolves into the mixture. The coating is then applied to the stent and upon application, curing and drying, including evaporation of the solvent, the dexamethasone remains dispersed in the coating layer. It is believed that the coating is somewhat in the nature of a solid solution of recrystallized particles of dexamethasone in silicone rubber. Dexamethasone, as a rather small molecule, however, does not need gross pores to elute and may be transported or diffused outward through the silicone material over time to deliver its anti-inflammatory medicinal effects.

The coatings can be applied by dip coating or spray coating or even, in some cases, by the melting of a powdered form in situ or any other technique to which the particular polymer/biologically active agent combination is well suited.

It will be understood that a particularly important aspect of the present invention resides in the technology directed to the incorporation of very fine microparticles or colloidal suspensions of the drug into the polymer matrix. In the case of a crystalline drug, such as heparin, the drug release is controlled by the network the drug forms in the polymer matrix, the average particulate size controlling the porosity and so the ultimate elution rate.

Figure 4A depicts a stent which has been spray coated with a solvent containing a cured polysilicone material including an amount of heparin crystals to provide a thin, uniform coating on all surfaces of the stent. The coated stent was cured at 150°C for 18 minutes; The sample was eluted in PBS for 49 days at 37°C and the stent was rinsed in ethanol prior to taking the scanning electron microscope picture of Figure 4A. Figure 4B shows a greatly enlarged (600X) scanning electron microscope photograph (SEM) of a portion of the coating of Figure 4A in which the microporosity is evident. The coating thickness may vary but is typically from about 75 to about 200 microns.

Figures 5A and 5B show scanning electron microscope photographs of a heparin containing polysiloxane stent. The Figure shows the coating prior to elution of the heparin. The coating was cured at 150° for 18 minutes. Figure 5B is greatly enlarged photograph (SEM) of a fragment of the coated surface of Figure 5A showing the substantially non-porous surface prior to elution.

Figures 6A and 6B show the posture of a stent in accordance with the invention as implanted in a swine coronary. The blemish shown in Figure 6A represents a histological artifact of unknown origin. As can be seen in Figure 6B, the general texture of the heparin-containing silicone material appears as a relatively open matrix containing a large number of gross pores.

The substantially non-porous surface of Figure 7A typically occurs with an incorporation of an amount of non-particulate material such as dexamethasone which partially or entirely dissolves in the solvent for the poly siloxane prior to coating and cure. Upon curing of the polymer and evaporation of the solvent, depending on the loading of dexamethasone, the dexamethasone reprecipitates in a hydrophobic crystalline form containing dendrite or even elongated hexagonal crystals approximately - 5 microns in size.

As can be seen in Figure 7B, even after release of the incorporated material or three months, the coating surface remains substantially non-porous indicating the transport or diffusion of the drug outward through the silicone material neither requires nor produces gross pores. The dexamethasone is incorporated in its more hydrophobic form rather than in one of the relatively more hydrophilic salt forms such as in a phosphate salt, for example.

Figures 8 and 9 depict plots of total percent drug release related to long-term drug release stent coating layers. Figure 8 depicts the release of heparin from a 50% heparin loading in silicone. The silicone was cured at 90°C for 16 hours. The

heparin release took place in a phosphoric buffer (pH=7.4) for 90 days at 37°C. The heparin concentration in the phosphoric buffer was analyzed by Azure A assay.

Figure 9 depicts a graphical analysis, similar to that depicted for heparin in Figure 8, for the release of dexamethasone at two different concentrations, i.e., 5% and 10% in silicone polymer. The coated stents were cured at 150°C for 20 minutes and the release took place in a polyethylene glycol (PEG), MW=400/water solution at 37°C ((PEG 400/H_2O) (40/60, vol/vol)). The dexamethasone concentrations were analyzed photometrically at 241 μm.

Figures 8 and 9 illustrate possible stent layer polymer/bioactive species combinations for long-term release. As stated above, the release rate profile can be altered by varying the amount of active material, the coating thickness, the radial distribution of bioactive materials, the mixing method, and the crosslink density of the polymer matrix. Sufficient variation is possible such that almost any reasonable desired profile can be simulated.

As stated above, while the allowable loading of the elastomeric material with heparin may vary in the case of silicone materials, heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or

more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

CLAIMS

We claim:

1. A stent for implantation in a body comprising a tubular metal body having open ends and an open lattice sidewall structure and a layer on the surface of said sidewall structure, said layer comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom.

2. The device of claim 1 wherein said tubular body is formed of an open braid of filaments of fine metallic wire which is axially deformable for insertion but which resumes a predetermined diameter and length upon relaxation.

3. The device of claim 2 wherein the metal is selected from the group consisting of stainless steel, titanium alloys including nitinol, tantalum, and cobalt-chrome alloys.

4. The device of claim 1 wherein said layer is applied as a solvent mixture of uncured polymeric material and finely divided biologically active species and then cured at an elevated temperature.

5. The device of claim 4 wherein the biostable elastomeric material is selected from the group consisting of silicones,

polyurethanes, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and combinations thereof.

6. The device of claim 1 wherein said elastomeric material is a poly siloxane and wherein said biologically active material is selected from the group consisting of heparin and dexamethasone.

7. The device of claim 6 wherein said biologically active material is heparin having an average particle size ≤10 microns.

8. The device of claim 7 wherein the amount of heparin is from about 10% to about 45% of the total weight of the layer.

9. The device of claim 7 wherein said layer is from about 30 to about 150 μm in thickness.

10. The device of claim 4 wherein said biologically active species is at least partially soluble in said solvent mixture of uncured polymeric material.

11. The device of claim 10 wherein said biologically active species is dexamethasone and comprises from about 0.4% to about 45% of the total weight of the layer.

12. The device of claim 2 wherein said coating adheres to the filaments of fine metallic wire in a manner that preserves said open braid.

13. The device of claim 6 wherein said coating adheres to the filaments of fine metallic wire in a manner that preserves said open braid.

14. A tubular stent for implantation in a body lumen location of interest comprising a flexible, elastic open braided tubular body of relatively fine metallic wire, said body being coated with a thin layer of a biostable hydrophobic biologically inactive elastomeric material selected from the group consisting of silicones, polyurethanes, thermoplastic elastomers, ethylene vinyl acetate copolymers, and EPDM rubbers, containing an amount of finely divided biologically active material dispersed therein in a manner that produces a controlled delivery of said biologically active species from said stent upon implantation, said coating adhering to the individual filaments of said braided structure in a manner that preserves said open braided structure.

15. A stent for implantation in a body comprising a tubular metal body having open ends and an open lattice sidewall structure and a layer on the surface of said sidewall structure, said layer comprising a hydrophobic elastomeric material containing biologically active material therein, the layer adapted to provide

long-term delivery of said biologically active material in the body.

16. The device of claim 15 wherein the hydrophobic elastomeric material is selected from the group of silicones, polyurethanes, ethylene vinyl acetate copolymers, polyolefin elastomers, and EPDM rubbers and combinations thereof.

17. The device of claim 15 wherein said elastomeric material is a poly siloxane and wherein said biologically active material is selected from the group consisting of heparin and dexamethasone.

18. The device of claim 15 wherein said biologically active material is heparin having an average particle size ≤10 microns.

19. The device of claim 15 wherein said biologically active species is dexamethasone and comprises from about 0.5% to about 10% by weight of said coating.

20. The device of claim 15 wherein said tubular body is formed of an open braid of filaments of fine metallic wire, and said coating adheres to the filaments of fine metallic wire in a manner that preserves said open braid.

DRUG RELEASE COATED STENT

ABSTRACT OF THE DISCLOSURE

The disclosure relates to a stent for implantation in a body lumen location of interest in a patient and includes a generally flexible elastic, tubular body having open ends and a thin open porous sidewall structure and a relatively thin coating layer on the tubular body including a biostable elastomeric material incorporating an amount of biologically active material dispersed therein for timed delivery therefrom.

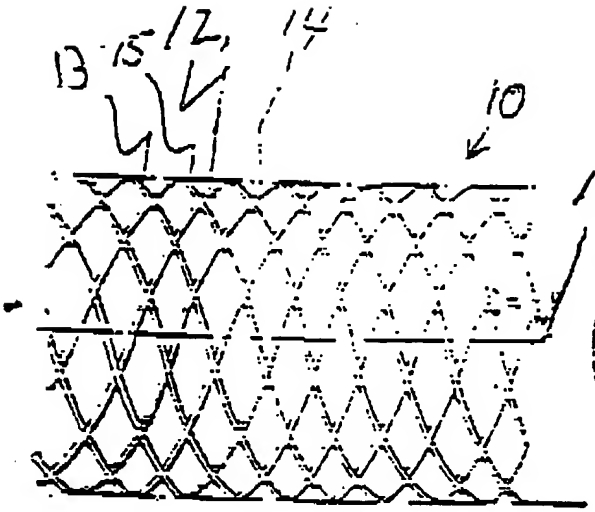


Fig 1A

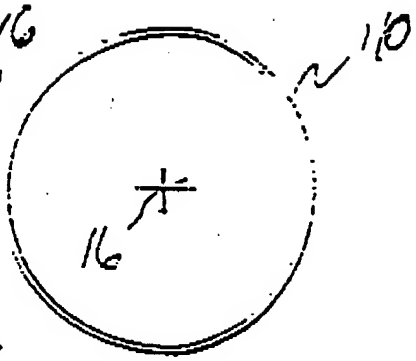


Fig 1B

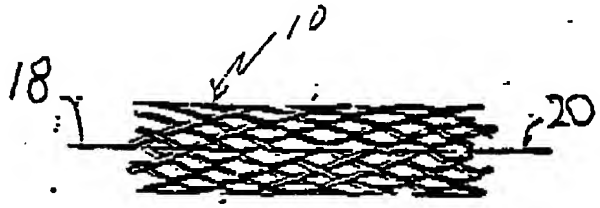


Fig 2A

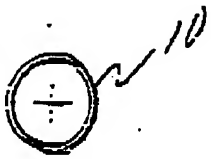


Fig 2B

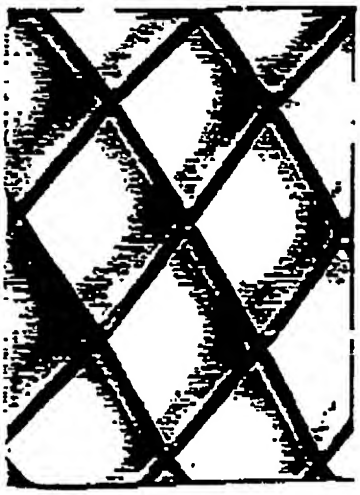


Fig 3

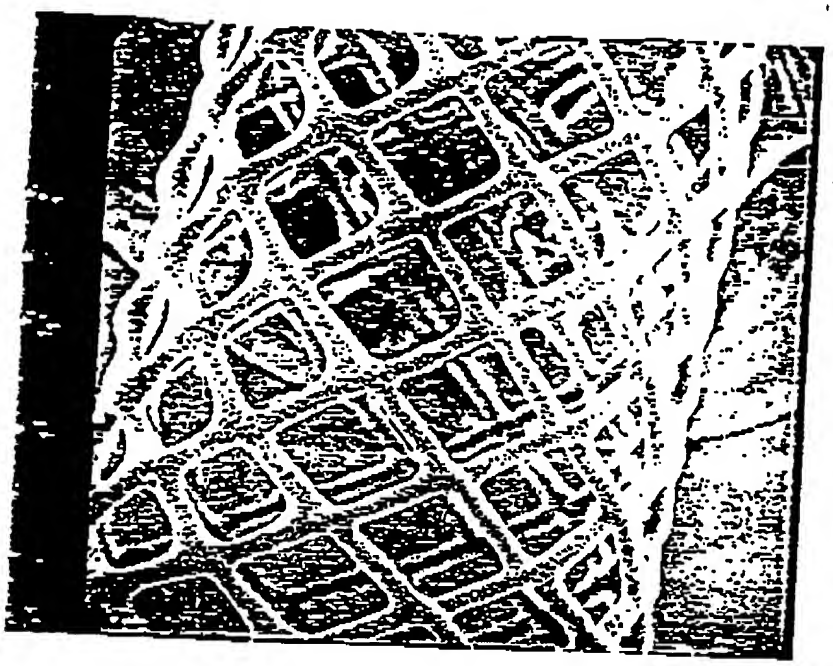


Fig 4A

50H, coated on 5/5/94, 150°C for 18 min. Released in PBS for 49 days at 37°C. EtOH rinse before SEM. x20

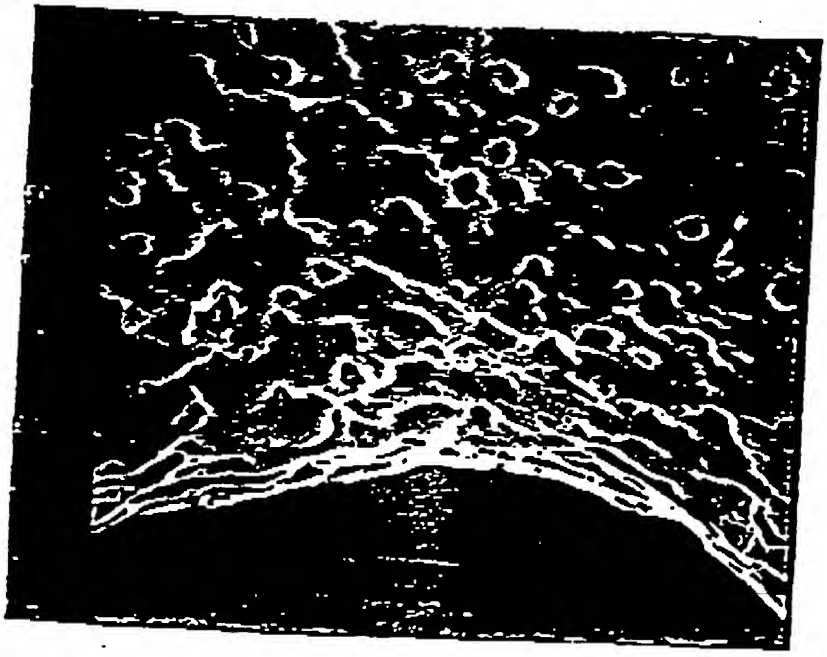


Fig 4B

50H, coated on 5/5/94, 150°C for 18 min. Released in PBS for 49 days at 37°C. EtOH rinse before SEM. x500

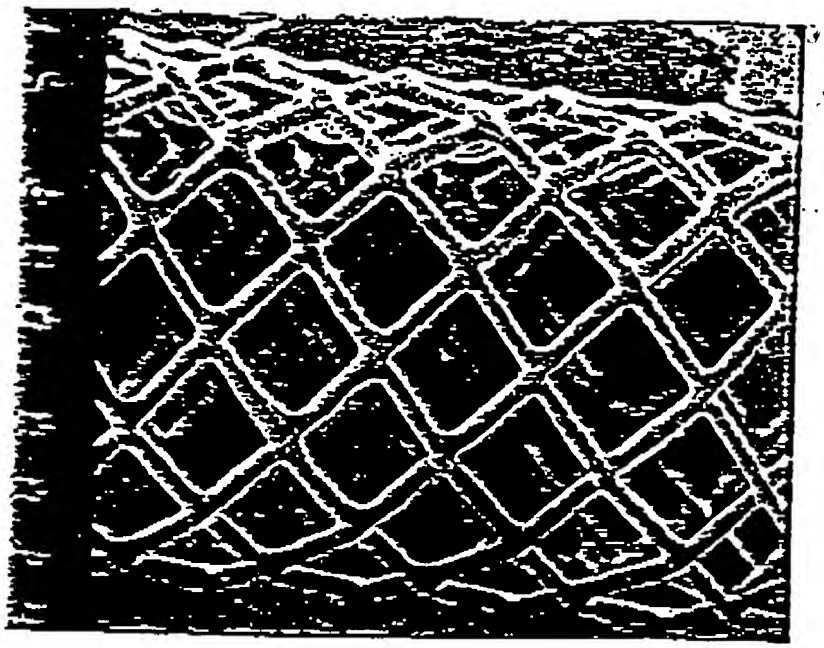


Fig 5A

SOHL coated on 5/5/94, 150°C for 13 min. No rinse before SEM x20

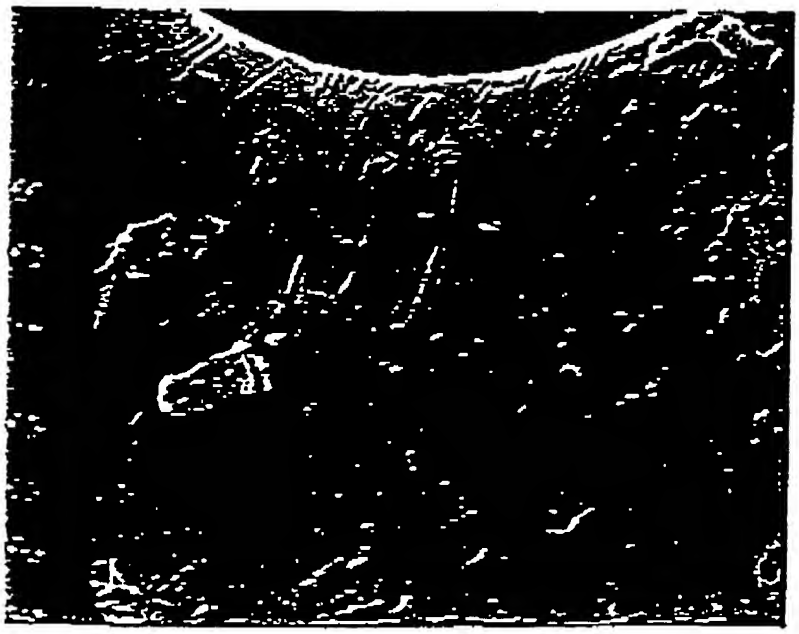


Fig 5B

SOHL coated on 5/5/94, 150°C for 13 min. No rinse before SEM x200

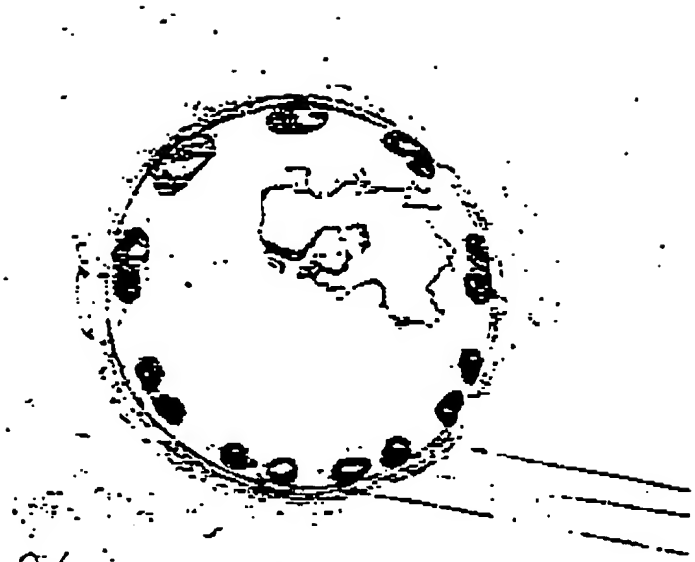


Fig 6A

Fig 6B

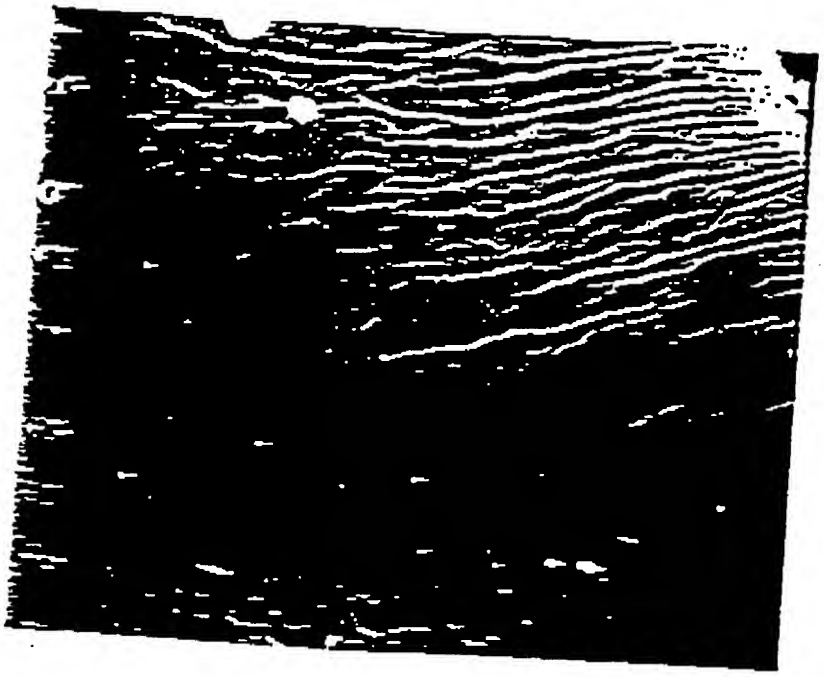


Fig 7A

SEDEX coated on 6/30/94. 90°C for 16 hrs. No rinse before SEM. x500

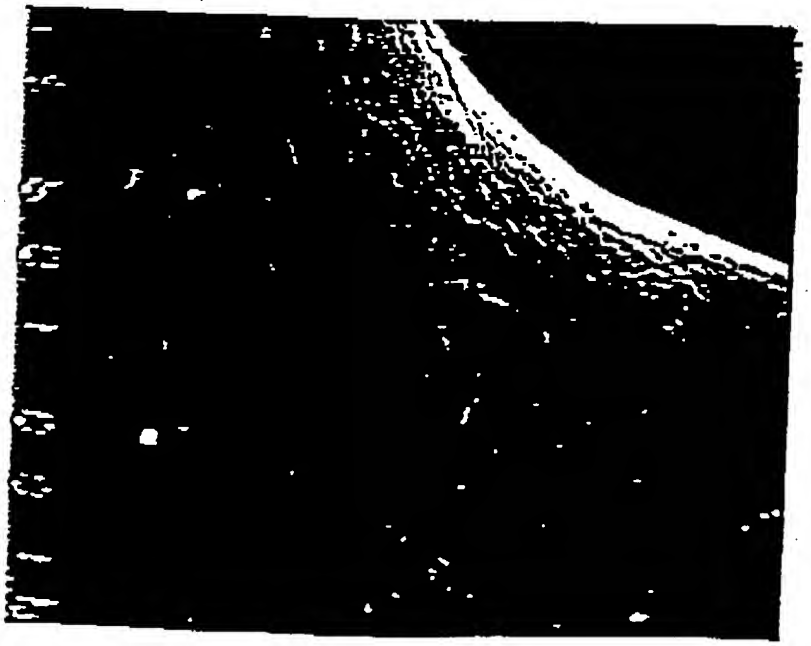


Fig 7B

SEDEX coated on 6/30/94. 90°C for 16 hrs. Refluxed in PEG 400/H_2O for 3 hrs. No rinse before SEM. x500

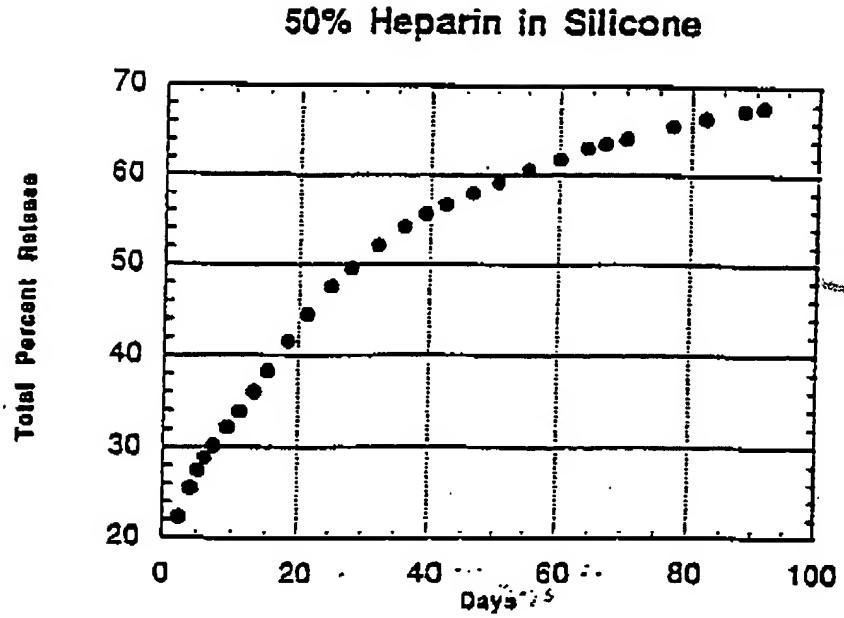

50% Heparin in Silicone
Total Percent Release
70
60
50
40
30
20
0
20
40
60
80
100
Days

FIG 8

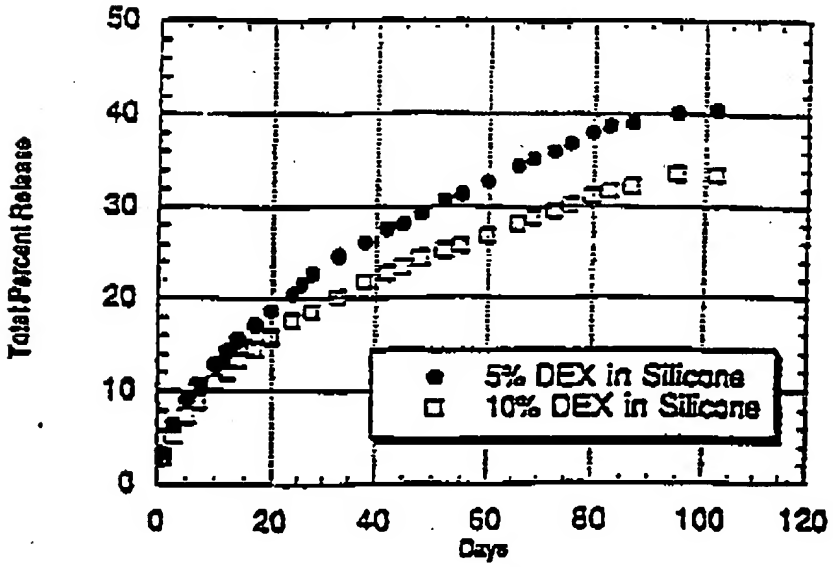

Total Percent Release
50
40
30
20
10
0
0
20
40
60
80
100
120
Days
5% DEX in Silicone
10% DEX in Silicone

FIG 9